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09/108,673	07/01/1998	CHIN-LEOU TENG	ISIS-3105	2703

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PAUL K LEGAARD
WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS
ONE LIBERTY PLACE 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	37

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/108,673	Teng et al
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 22, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *25-27, 44-50, 53-55, 57-64, 66-77, and 79-82* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-27, 44-50, 53-55, 57-64, 66-77, and 79-82* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 36
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. The declaration of Dr. Teng under 37 CFR 1.132 filed January 22, 2002 is insufficient to overcome the rejection of claims 25-27, 40 and 61-81 based upon as set forth in the last Office action because: The data presented show that lauric acid produced a 0.9% increase in DNA uptake when used alone, and capric acid produced an 8.3% increase in DNA uptake when used alone. Then the data showed that a combination of capric acid and lauric acid produced an 11% increase in DNA uptake when used in combination. The purely additive expectation of capric acid and lauric acid is therefore 9.2%. The data presented in the declaration does not present the percent error in the measurements, and does not show any statistical data to show that the 11% increase is statistically significant over the expected additive value of 9.2%. The increase of 11% over 9.2% is less than 120% increase. Biological experiments with error rates of 25% are commonplace, and no clear evidence has been presented that an increase of less than 20% over the expected result is indeed an unexpected result. Therefore the sparse data presented in the declaration is insufficient to prove the assertion of unexpected results.

Response to Arguments

2. Amendments to claims 40, 50, 63 and 74 in Paper No. 34, filed January 22, 2002 have overcome the rejection of the claims regarding the word "modulates" under 35 USC 112, first paragraph in the previous office action, and the rejection is withdrawn.

3. Amendments to the specification in Paper No. 34 have overcome the objection to the specification in the previous office action, and the rejection is withdrawn.

4. Amendments to the claims in Paper No. 34 have overcome the rejection of the claims under 35 USC 112, second paragraph in the previous office action, and the rejection is withdrawn.

5. Arguments in Paper No. 34 have overcome the rejection of the claims under 35 USC 103 in the previous office action, and the rejection is withdrawn.

6. Arguments filed in Paper No. 34 regarding the rejection of claims 25-27, 40 and 66-81 under 35 USC 112, first paragraph in the previous office action are not found convincing and the rejection is sustained. The response to the arguments is contained in the rejection repeated below.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 25-27, 40, 66-77 and 79-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of use of a composition containing an antisense nucleic acid in an animal. The specification is directed to a method of treating and a method of investigating the role of a gene or gene product in an animal having or suspected of having a disease or disorder that is treatable in whole or in part with one or more nucleic acids delivered to the animal via the enteral route.

The Specification does not teach one of ordinary skill in the art how to use an antisense nucleic acid in a method to treat or investigate the role of a gene or gene product in an animal (which may be other than a human). Treatment with antisense nucleic acids is a new and developing art involving gene therapy which is highly unpredictable. While the Specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway which is a step toward a method of treatment with antisense nucleic acids, it does not teach one of ordinary skill in the art how to treat nor investigate a role of a gene or gene product with antisense nucleic acids since the practice of the treatment or investigation is highly unpredictable, and would require specific teachings to guide

the ordinary skilled artisan how to make and use the claimed invention. As such, specific teachings must be present in the Specification to support any claims to treatment or investigation in an animal with an antisense nucleic acid. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivery via the enteral route of an antisense nucleic acid to an animal and predictably treating or investigating the role of the delivery of the antisense nucleic acid in the animal. Treatment of an animal with an antisense nucleic acid is a new and developing art, and as such requires detailed teachings on how to make and use such a nucleic acid.

b- The specification teaches the delivery of a nucleic acid via the enteral route to the blood and generally into the internal organs of an animal by cannula delivery of nucleic acids to the small intestine of a rat. There are no teachings of treatment or investigation of the role of a gene or gene product with an antisense nucleic acid.

c- The nature of the invention is complex. Treatment of animals with antisense nucleic acids is a new and developing art as taught in Gewirtz et al. (see the entire article). Gewirtz et al. taught the difficulties of therapy with nucleic acids such as antisense oligodeoxynucleotide, stating that there are two major problems which must be overcome. First, the nucleic acid must

find its cellular target. Second, it must then find and act on its intracellular target. The specification does not teach one of ordinary skill in the art how to direct the nucleic acid to its cellular target nor how the nucleic acid would then act on its intracellular target.

d- The state of the prior art as taught by Gura (see especially page 575, column 1, second paragraph, and page 576, third paragraph to the end of the article) demonstrates some of the difficulties associated with nucleic acid pharmaceutical therapy, stating "[b]ut the biggest concern is that antisense compounds simply don't work the way researchers once thought they did"...."Besides not always working by 'true antisense mechanisms,' the synthetic oligonucleotides have also caused side effects in experimental animals."

e- The state of the art as recited in Stull et al. (see especially pages 476-478) taught that the stability, affinity, efficiency and subcellular distribution of the nucleic acids in the host animal are all areas of uncertainty and need careful study and analysis before any nucleic acid therapeutic modality can be understood and consistently applied. Also, Agrawal et al. taught the delivery of synthetically modified nucleic acids administered to rats via the oral route. However, the nucleic acids had been specifically modified to resist nuclease digestion. Also, no effect on genes or gene products was demonstrated by Agrawal et al. Agrawal et al. (Molecular Medicine Today, Vol. 6, pp 72-81, February 2000, at the Introduction and "Cellular uptake facilitators for in vitro studies" at pages 79-80) teach that antisense molecules are unpredictable in their use for in-vivo applications.

f- The teaching of absorption into the blood and internal organs of the nucleic acids in the instant Specification does not demonstrate any targeting of the nucleic acid to a cell or to intracellular targets as recited by Gewirtz et al., nor does the Specification address any of the issues raised by Gura or Stull et al. Therefore, no pharmaceutical effect has been demonstrated.

g- Branch et al. (TIBS, Feb. 1998) teach at the abstract that antisense is "difficult to produce" and "their ability to eliminate the function of a single gene has never been proven". For the reasons stated by Gewirtz et al., Gura, and Stull et al. Agrawal et al. and Branch the unpredictability of pharmaceutical applications of nucleic acids is very high.

h- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

10. Arguments set forth in Paper No. 34, page 8 assert that the invention defined by the claims must be enabled, and that not all inventions set forth in the specification need be enabled. This is true. The invention as set forth in the claims is not enabled as discussed above. Delivery of an antisense nucleic acid to the alimentary canal of an animal lacks a utility per se. The delivery of an antisense nucleic acid across the intestinal mucosa also does not have a utility, since the purpose of delivering an antisense nucleic acid across the intestinal mucosa is one step in the delivery of the antisense nucleic acid for some real-world purpose, such as the stated

treatment or investigation of the role of a gene or gene product. Therefore, lack of enablement does not concern delivery of an antisense across the intestinal mucosa.

11. The issue of the declaration of Dr. Teng is discussed above.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 61 is rejected under 35 U.S.C. 102(b) as being anticipated by Kitao.

Kitao taught a composition comprising a nucleic acid and capric or lauric acid in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claim 61 is rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/05903.

WO 97/05902 (see especially page 5) taught a composition comprising a nucleic acid and capric in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29; 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 25-27, 44-47, 49, 50, 53-55, 57-59, 61-64, 66-71, 73-77 and 79-82 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,707,648.

US 5,707,648 (see especially columns 3-8, 12-15 and the claims) taught a composition comprising a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue and a method of using the composition for (delivering) enhancing penetration of an antisense nucleic acid across the alimentary canal. The nucleic acid may be modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage or a 2'-methoxy modification. The delivery may be sublingual, oral, endoscopic or rectal. The two fatty acids may be capric acid and lauric acid. The composition may further comprise a carrier compound. The nucleic acid may be an antisense nucleic acid which decreases the expression of a cellular adhesion protein or the rate of cellular proliferation. The composition may be water based, propylene glycol based and may comprise less than about

8% water. The composition may further comprise a bile salt. The oligonucleotide may be in the form of a prodrug.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 25-27. 44-50, 53-55, 57-64, 66-77 and 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of US 5,707,648 in view of US 5,843,738.

The claims are drawn to a composition comprising a nucleic acid and at least two fatty acids in a pharmaceutically acceptable form, wherein the nucleic acid has a modified nucleobase or modified sugar residue and a method of using the composition for (delivering) enhancing penetration of an antisense nucleic acid across the alimentary canal. The nucleic acid may be modified with a 5-methyl-cytosine substitution, a phosphorothioate linkage or a 2'-methoxy modification. The delivery may be sublingual, oral, endoscopic or rectal. The two fatty acids may be capric acid and lauric acid. The composition may further comprise a carrier compound. The nucleic acid may be an antisense nucleic acid which decreases the expression of a cellular adhesion protein or the rate of cellular proliferation. The composition may be water based, propylene glycol based and may comprise less than about 8% water. The composition may

further comprise a bile salt. The oligonucleotide may be in the form of a prodrug. The carrier compound may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

US 5,707,648 taught the invention as described above in the rejection under 35 USC 102.

US 5,707,648 did not teach that the carrier compound may be polyinosinic acid, dextran sulfate, polycytidylic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'-disulfonic acid.

US 5,843,738 taught (see especially columns 9-10 and example 20) the inclusion of dextran sulfate in a composition of antisense nucleic acid delivered in a composition containing fatty acids via the alimentary canal where the nucleic acid may be modified in its nucleobase or sugar residue.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of US 5,707,648 with US 5,843,738 to produce the instant claimed invention because each of US 5,707,648 with US 5,843,738 taught the delivery of nucleic acids to the alimentary canal of an animal in a composition containing fatty acids. US 5,843,738 provides teachings of using dextran sulfate in the method for the benefit of producing a condition which may be treatable by the antisense nucleic acid.

One of ordinary skill in the art would have been motivated to combine the teachings of US 5,707,648 with US 5,843,738 to produce the instant claimed invention because US 5,483,738 taught that the addition of dextran sulfate in the composition induces a condition which may be counteracted by the addition of the antisense nucleic acid, to show that an experimentally

induced condition is preventable by the addition of the antisense nucleic acid. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US 5,707,648 with US 5,843,738.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If

applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

July 10, 2002

TERRY MCKELVEY
PRIMARY EXAMINER